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Catheter-Directed Thrombolysis vs. Pharmacomechanical Thrombectomy for Upper Extremity Deep Venous Thrombosis: Cost-Effectiveness Analysis

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ABSTRACT

Background and Aims: We compared the immediate and one-year results as well as total hospital costs between catheter-directed thrombolysis (CDT) and pharmacomechanical thrombolysis (PMT) in the treatment of symptomatic upper extremity deep venous thrombosis (UEDVT).

Material and Methods: From 2006 to 2013, 55 patients with UEDVT were treated with either CDT or PMT at Helsinki University Hospital. Of them, 43 underwent thoracoscopic rib resection later in order to relieve phlebography-confirmed vein compression. This patient cohort was prospectively followed up with repeated phlebographies. CDT was performed to 24 patients and 19 had PMT with a Trellis™ device. Clinical evaluation and vein patency assessment were performed with either phlebography or ultrasound one year after the thrombolysis. Primary outcomes were immediate technical success, one-year vein patency, and costs of the initial treatment.

Results: The immediate overall technical success rate, defined as recanalization of the occluded vein and removal of the fresh thrombus, was 91.7% in the CDT group, and 100% in the PMT group (n.s.). The median thrombolytic time was significantly longer in CDT patients than PMT patients (21.1 hours vs. 0.33 hours, P<0.00001). There were no procedure-related complications. The one-year primary assisted patency rate was similar in both groups (91.7% and 94.7%, respectively). There were no recurrences of clinical DVT. The hospital costs for the acute period were significantly lower in the PMT group than the CDT group (medians 11,476 € and 5,975 € in the in the CDT and PMT group, respectively (P<0.00001)).

Conclusions: The clinical results of the treatment of UEDVT with CDT or PMT were similar. However, PMT required shorter hospital stay and less intensive surveillance, leading to lower total costs.

Key words: Upper extremity deep venous thrombosis, thrombolysis, thrombectomy, catheter-directed thrombolysis, pharmacomechanical thrombectomy

INTRODUCTION

Upper extremity deep vein thrombosis (UEDVT) represents approximately 2–3% of all deep vein thromboses (1). Primary UEDVT includes idiopathic and effort-related thrombosis (Paget–Schroetter syndrome). Effort-related UEDVT may be related to abnormal anatomy, or it may be a consequence of strenuous activity (2). Secondary UEDVT is mostly related to central venous catheters, pacemaker devices, or malignancy (3).

The clinical manifestations of UEDVT include edema of the affected extremity in 80%, extremity pain in 30%–50%, and erythema in approximately 15% of the patients (4). Approximately 5% of patients have no symptoms (5,6). The incidence of post-thrombotic syndrome (PTS) in the upper limb ranges from 7% to 46%, and PTS may result in significant morbidity, especially if it occurs in the dominant arm (7). Treatment with anticoagulant therapy alone is associated with delayed resolution of acute symptoms, reduced venous outflow, and increased incidence of residive thrombus, chronic venous obstruction, venous valvular incompetence, and subsequent venous hypertension (8). Systemic thrombolysis has been associated with major hemorrhagic problems. In order to reduce the thrombolytic therapy dose and the bleeding risk, American College of Chest Physicians (ACCP) guidelines encourage catheter-based thrombolysis over systemic infusion in treatment of UEDVT with severe symptoms; with thrombus extending most of the subclavian and the axillary vein, symptoms for <14 days, good functional status, life expectancy of > 1 year, and a low risk for bleeding (9).

CDT has also been associated with major systemic hemorrhage, and long infusion times (8). PMT with the Trellis™ device (Trellis™ Peripheral Infusion System, Covidien, Mansfield, MA, USA) intended to overcome these disadvantages by combining mechanical clot disruption and pharmacological

thrombolysis within an isolated zone. However, due to problems with the sterilization process and errors in marking of the balloons, Trellis was withdrawn from the market in xxxx. The current study was conducted prior to the withdrawal. To our knowledge, this is the only study comparing PMT and CDT for UEDVT.

We report the immediate and mid-term results as well as the total hospital costs between conventional CDT and PMT with the Trellis™ device in the treatment of symptomatic UEDVT.

MATERIAL AND METHODS

From 2006 to 2013, 72 patients with UEDVT were seen at the Helsinki University Hospital. All patients were clinically assessed and duplex ultrasonography (DUS) was used as the primary diagnostic method. The coagulation profile was assessed at the time of the first visit. Computed tomography (CT) and magnetic resonance imaging (MRI) were used in patients with inconclusive duplex data or if a pulmonary embolism was suspected. Of the 72 patients, 17 with minimal symptoms were treated conservatively using low-molecular-weight heparin (LMWH), and 55 patients with more severe symptoms were treated invasively, with either CDT or PMT using the Trellis™ device. After CDT/PMT, all patients underwent completion phlebography with provocation tests in order to assess the technical success and completeness of the thrombolysis/thrombectomy, as well as a possible vein compression. Technical success was defined as successful recanalization of the occluded vein and removal of the fresh thrombus. Completeness of the thrombolysis/thrombectomy was graded to three classes: “complete” if phlebography showed no further clot, “partial” if thrombolysis was incomplete, but less than 50% of the thrombus remained, and “failed” when more than 50% of the thrombus was present after the intervention (11,12). To detect compression, phlebography was performed both at rest (full adduction) and at provocation (arm 90 degrees abducted with external rotation “hand-on-head position”).

As a second stage procedure, forty three (78.2%) of 55 patients who underwent early clot removal underwent a thoracoscopic first rib resection due to an external compression of the vein detected in post-thrombolysis phlebography (13). They were included in a prospective rib resection surveillance program, which was analysed retrospectively from hospital records. The surveillance protocol included both clinical control and patency examinations with DUS and phlebography, as well as an assessment for the need for PTA based on the presence of symptoms and stenosis >20% or occlusion.

Twelve (12%) of the 55 patients underwent local thrombolysis only with no rib resection and were excluded, because there was no systematic follow-up imaging available for these patients. The reasons being malignancy in 2 patients, lack of extrinsic compression in control phlebography in 5 patients, local foreign material (pacemaker) in 2 patients, and chronic occlusion of the subclavian vein in 3 patients (all three had thrombophilia and minimal or no symptoms after CDT) (Figure 1).

Twenty-four of the study patients underwent CDT and 19 had PMT. In the beginning of the study period, in 2006 until 2012, CDT was used routinely. Since 2012, the Trellis™ device was introduced in our institution and became more popular. Patient selection was thus partly time-dependent; and, towards the end of the study period, depended upon whether the radiologist performing the procedure was familiar with the PMT procedure or not. Phlebographic images obtained at the time of treatment and during the follow-up were carefully reviewed.

To assess mid-term results, one-year duplex scan reports as well as phlebography images and reports were evaluated. Duplex scan only was performed to 25 patients, phlebography only to 12 patients and both duplex and phlebography to 6 patients mostly due to inconclusive result of duplex. In the end the mid term patency assessment was based on duplex scan in 25 cases and phlebography in 18 patients.

The end points were immediate technical success and one-year vein patency. Successful PTA was defined as residual stenosis of 0-20%.

The detailed hospital costs for all patients during lysis admission time were collected from the hospital cost database (Financial administration services of the Department of Surgery, Helsinki University Hospital).

Treatment options

A Catheter-directed thrombolysis

Percutaneous access was achieved with ultrasound guidance primarily through the basilic vein and secondarily through the cephalic, brachial, or cubital veins, using a 4-French sheath. A 0.035'' hydrophilic wire (Radiofocus guide wire M, Terumo Co., Japan) was passed through in the CDT group, and a diagnostic phlebography was performed to assess the lesion, its extension, and the presence of collaterals.

A single dose of alteplase (10 mg) was administered through a multi-hole catheter (tähän katetrin tiedot) into the occlusion, and infusion at a rate of 1 mg/hour was started. The patient was observed at the intermediate care unit. After approximately 24 hours of thrombolysis, a second phlebography was performed to assess the lytic success and the need to continue thrombolysis for an additional 24 hours. In the final phlebography, the need for balloon angioplasty was assessed and in case of a significant stenosis a 8-12mm balloon was used (Figure 2).

B Pharmacomechanical thrombectomy

The access technique and assessment of the lesion were similar to the CDT procedure. The Trellis™ catheter was positioned over a 0.035" guide wire through an 8-Fr sheath, leaving the area of treatment between the two inflated balloons. Thereafter, 6–10 mg of alteplase was injected through the side holes of the device catheter and a rotational technique started to disrupt the thrombus. For the next 10–20 minutes, alteplase was injected slowly to promote thrombolysis. Finally, the melted thrombosis was aspirated with a 50-ml syringe through the side hole and the vein was evaluated with a manual injection of contrast media. After the first session, if thrombolysis was not complete, the pharmacomechanical

lysis was continued using 6–10 mg of alteplase for another 10–20 minutes. The maximum amount of alteplase was 20 mg. Seventeen (89%) patients had a single-session lysis. In 16 patients, the lysis lasted for 20 minutes and for 3 patients, 10 minutes due to a short occlusion with a small thrombus. Two (11%) patients required 2 sessions lasting a total of 30–35 minutes. Completion phlebography, possible PTA and anticoagulation were similar to the CDT group. Patients treated with PMT had no need for a stay in an intermediate care unit.

Low molecular weight heparin was started with a dose 1mg/kg twice a day immediately when the diagnosis was made and continued during the CDT and PMT. After thrombolysis, the patients were kept on LMWH and warfarin until the INR reached 2–2.5, after which warfarin treatment was continued for 3–6 months.

The surgical decompressions were later performed with a video-assisted thoracoscopic first rib resection (VTRR) technique. The procedure is described in detail elsewhere (13).

Statistical analysis

SPSS 22.00 was used in the statistical analysis. Continuous variables are expressed as median values (range). The prevalence of risk factors is expressed as percentages. Comparisons between the groups were made using the Mann–Whitney U test (continuous variables) and chi-square test (dichotomic variables).

The study protocol has been accepted by the Institutional Review Board (HUS/214/2016). Because of the retrospective nature of this study, no informed consent was obtained from the study subjects.

RESULTS

The CDT group included 24 patients with a median age of 31 years, and the PMT group included 19 patients with median age of 26. There were no significant differences in patient demographics between the groups. The most common symptoms were swelling, pain, and numbness of the affected extremity, with an equal prevalence in the groups (Table I). Duplex US was used as the first diagnostic examination in 41 patients (95%), while additional imaging was employed in 5 (12%): MRI in 2, and CT in 3 patients. The median time between symptom onset and intervention was 4.5 days (range 1–12 days) and 4 days (range 1–7 days) in CDT and PMT groups, respectively (n.s.). The median thrombosis length in treated patients with Trellis™ was 116 mm (range 30-225 mm), and in the CDT group the median lesion length was 160.5 mm (range 45-254 mm). The median time from the early clot removal to the rib resection was 92 days (range, 10-458 days), 68.5 days (range, 15-458 days) in the CDT group and 120 days (range, 10-265 days) in the PMT group.

Immediate technical success

Immediate overall technical success was 92% and 100% in the CDT and PMT groups, respectively. In the PMT group, complete lysis was achieved in 17 (90%) and partial lysis in 2 (11%) patients. In the CDT group, the therapeutic response was complete in 19 (79%) and partial in 3 (13%) cases, while the treatment failed in 2 (8%). The residual lesion after thrombolysis and the change in the lesion's topography before rib resection are shown in Table II.

In 2 patients (8%), the treatment was started with CDT, but due to persistent thrombosis after two days of thrombolysis, PMT was successfully initiated to remove the residual thrombosis. Ten (42%) patients in the CDT group and 8 (42%) in the PMT group underwent balloon angioplasty due to moderate or

significant stenosis in the completion phlebography. The immediate phlebographic results are presented in Table II. There was no pulmonary embolism found in the CT scan in patients with a clinical suspicion of PE, or other major complications during the hospital stay after either of the procedures. The treatment parameters of the PMT and CDT patients are shown in Table III.

One-year follow-up for vein patency

After a median follow-up of 13 months (range 10–36), the vein patency was assessed either by phlebography (n=18) or duplex US (n=25). A good flow with no significant stenosis (<20%) was observed in 18 (75%) patients in the CDT group, and in 17 (90%) patients in the PMT group (n.s.). No significant difference in symptoms or technical success were seen at one year (Table IV). During the follow-up period, 11 (46%) patients in the CDT group and 10 (53%) patients in the PMT group (ns) underwent balloon angioplasty due to stenosis >20% or occlusion associated persistent symptoms (Table IV). No stents were used. The overall assisted primary patency at one year was 92% (n=22) in the CDT group and 95% (n=18) in the PMT group (ns). No patients suffered a recurrence of clinical DVT during the follow-up.

Total hospital costs

The median total procedural cost of the hospital stay per patient was 6,986 (range 6,100–8,564) € in the CDT group and 4,499 (range 3,782–5,120) € in the PMT group, P< 0.001. The median total hospital cost was 11,476 (range 8,468–17,467) €/patient in the CDT group and 5,975 (range 4,763–7,395) €/patient in the PMT group (P<0.001). (Table III).

DISCUSSION

In acute UEDVT, both CDT and PMT are effective treatment methods and work more quickly than anticoagulation in the recanalization of the occluded vein (8,10). Studies on the results of PMT are scarce. We report a consecutive case series of 43 patients with symptomatic UEDVT who underwent invasive treatment with either CDT or PMT using a Trellis™ device and a thoracoscopic rib resection thereafter. We compared the safety, efficacy, one-year results, and total hospital costs of the two treatment methods. We found that PMT was associated with a significantly shorter treatment time, as well as lower total hospital costs than CDT, with similar safety, efficacy, and one-year results. Furthermore, the immediate phlebographic success was more often successful after PMT.

Our results are comparable with those reported in previous publications comparing CDT and PMT, although the majority of the patients in these studies have had lower-extremity DVT (LEDVT) (10,14). Kim et al. compared CDT and PMT in the treatment of 23 UEDVT and 44 LEDVTs in 36 patients (14). Catheter-directed thrombolysis was performed in 40 cases and pharmacomechanical thrombectomy with an Angiojet rheolytic thrombectomy catheter in 27 cases. The mean duration of the treatment was significantly longer in CDT when compared to PMT—48 and 26 hours, respectively. In addition, the consumption of urokinase was significantly lower in PMT. The authors achieved complete clot lysis in 73% using CDT and 82% with PMT. Lin et al., in turn, compared CDT and PMT with an Angiojet rheolytic thrombectomy system in 98 patients (10). They reported complete lysis of the thrombus in 75% of the patients after PMT versus 70% after CDT (n.s.) and partial lysis in 25% and 30% of the patients, respectively.

The largest benefit of PMT in comparison to CDT is the need for minimal or no intermediate care unit treatment and a shorter hospital stay. None of our PMT patients needed to be admitted to an intermediate care unit, and they spent an average 3 days in the hospital. The CDT patients required an

average of 2 days of treatment in the intermediate care unit, which was the duration of thrombolysis; and the median length of the hospital stay was 6 days. Lin et al. reported somewhat longer treatment periods (10).

The delay between the onset of symptoms and treatment has an impact on the success of thrombus removal. If thrombolysis is performed within a few days, the primary success rate is close to 100%. After two weeks, the success rate decreases to 85%; and after 6 weeks, down to 50% (15,16). The ACCP guidelines recommend that local thrombolysis should be performed in patients with severe symptoms of recent onset (<14 days) if appropriate expertise and resources are available (9). In our study, the median time between symptom onset and intervention was approximately 4 days in both groups. Probably due to the relatively short delay, we had a high immediate technical success rate with an overall thrombus removal of 100% in the PMT group and 92% in the CDT group (n.s.).

In many studies, the major drawback of CDT therapy has been hemorrhagic complications, which have been related to prolonged treatment duration (17-23). Our CDT patients received a median of 21 hours' infusion of the thrombolytic agent, as opposed to 20 minutes in PMT patients. We did not observe any bleeding complications, probably due to the small sample size.

The aim of CDT and PMT is to open the occluded vein and achieve immediate relief of the symptoms. However, long-term patency of the treated vein is also important. If a significant stenosis persists in provocation phlebography, a risk of rethrombosis exists and our treatment of choice is to perform a thoracoscopic first rib resection, and a postoperative balloon angioplasty of the vein when appropriate (13,23). The focus of this paper was to compare two different treatment options in the acute phase. One-year vein patency and the need for PTA was equal between the groups. No stents were used in

these patients because even if data are sparse in the literature, stent fractures have been found to be common in this position (24).

We used the Trellis™ device to achieve PMT with no major difficulties or complications. Unfortunately, the device was later withdrawn from the market. However, other devices for pharmacomechanical thrombectomy are still available. The results with the Angiojet rheolytic (Possis Medical, Minneapolis, MN) thrombectomy device are comparable to ours (10,11). We have had good experiences with PMT, the main benefit being the savings in intermediate care, and are now looking for a suitable device for routine use.

The main limitation of our study is the small number of patients. Furthermore, the length of follow-up was limited. The treatments were performed during different time periods: CDT was used in the beginning of the study period and the method then changed to PMT, which was mostly used in the latter period. CDT has been performed in our institution for years in both upper and lower extremities and the procedure was familiar to all interventional radiologists. Alltogether 7 interventionalists was performing CDT in this material. However, as PMT was initiated during the study period, there might be some learning curve effect. However, when started, all PMTs were performed by 2 interventional radiologists made all except three Trellis PMTs in this study. ~~However~~, Otherwise nothing else in the treatment protocol changed; patients underwent similar rib resection after the initial treatment, and the medication after thrombolysis/thrombectomy was the same. In the beginning of this study, a phlebographic protocol before and after rib resection was designed, and we chose to include only patients with a complete phlebographic work-up.

297 **CONCLUSION**

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299 The immediate and one-year clinical results of the treatment of subclavian vein thrombosis with CDT
300 and PMT are equal. However, the need for admission to an intermediate care unit, hospital stay, as well
301 as multiple phlebographic sessions and prolonged thrombolysis, were significantly more infrequent in
302 patients treated with PMT than with CDT, leading to significantly lower total costs.

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362

363 **FIGURE LEGENDS**

364 **Figure 1.** Patient flow.

365 **Figure 2. A** Phlebography showing thrombosis of the axillo-subclavien segment. **B** Post-thrombolysis
366 control phlebography with patent veins and a partial success (less than 50% thrombus remaining). **C**
367 Angioplasty after local thrombolysis using PMT. **D** Mid-term phlebography with open veins.

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Table I. Demographic data and initial symptoms before thrombolysis. There were no significant differences between the groups.

	PMT	**CDT**
Number of patients	19	24
Age (median, IQR)	26 (17-54)	31 (23-49)
Male: Female	9:10	12:12
Effort history* n (%)	13 (68%)	21 (88%)
Thrombophilia n (%)	3 (16%)	4 (17%)
Family history n (%)	4 (21%)	5 (21%)
RT UL n (%)	12 (63%)	17 (71%)
LT UL n (%)	7 (37%)	7 (29%)
Arm pain	17 (90%)	22 (92%)
Arm swelling	19 (100%)	24 (100%)
Arm numbness	11 (58%)	14 (58%)
Arm weakness	2 (11%)	2 (8%)
Neck swelling	1 (5%)	2 (8%)
Dilated neck veins	1 (5%)	7 (29%)
Positive provocation test	15 (79%)	20 (83%)
Pulmonary embolism	0 (0%)	1 (4%)
Paresthesia	4 (21%)	7 (29%)

PMT, pharmacomechanical thrombolysis; CDT, catheter-directed thrombolysis;

RT UL, right upper limb; LT UL, left upper limb.

*Heavy upper limb exercise as a probable etiology.

Values are presented as No (%) unless otherwise indicated.

Table II. Phlebographic results.

Degree of success of lysis (11,12)	**PMT**	**CDT**	**p-value**
Complete lysis >99%	17 (90%)	19 (79%)	*NS*
Partial lysis (50%-99%)	2 (11%)	3 (13%)	*NS*
Unsatisfactory lysis <50% / change line of treatment	0 (0%)	2* (8%)	*NS*
Degree of residual stenosis after thrombolysis			
No lesion/stenosis <20%	13 (68%)	7 (29%)	0.010
Moderate stenosis 20%-49%	4 (21%)	5 (21%)	*NS*
Significant stenosis 50%/>50%	2 (11%)	10 (42%)	0.024
Occlusion	0 (0%)	2 (8%)	*NS*
Pre-rib resection phlebographic findings **			
No lesion/stenosis <20%	14 (74%)	8 (33%)	0.009
Moderate stenosis 20%-49%	2 (11%)	3 (13%)	*NS*
Significant stenosis 50%/>50%	3 (16%)	10 (42%)	*NS*
Occlusion	0 (0%)	3 (13%)	*NS*
Re-thrombosis (pre rib resection)	0 (0%)	0 (0%)	*NS*

NS, not significant; *CDT*, catheter directed thrombolysis; *PMT*, pharmacomechanical thrombectomy.

*****Changed to Trellis

******This phlebography was done prior to thoracoscopic first rib resection (median time from thrombolysis to rib resection was 90.5 days, range 10–450 days).

[#]*P*-value=0.011, tested with chi-square for the combined numbers of significant and occlusions.

Values are reported as No. (%).

Table III. Treatment parameters, use of recources and costs in patients treated with PMT and/or CDT.

Treatment group	**PMT**	**CDT**	***P* value**
Infusion time	0.33 h (0.17–0.58 h)	21.12 h (16.11–47.25 h)	< 0.00001
Total alteplase dose	6 mg (6–15 mg)	32 mg (20–55.3 mg)	< 0.00001
Intermediate care unit (h)	0	48 h (48–72)	< 0.00001
Number of phlebographies	1	2 (2–3)	< 0.00001
Angiography and/or Interventional suite costs	4499.00 € (3782€-5120€)	6985.50 € (8564€-6100€)	< 0.00001
Length of hospital admission	3 days (1–8 days)	6 days (3–15 days)	0.0061
Total hospital costs	5975.00 € (4763€–7395€)	11476.00 € (8468€–17467€)	< 0.00001

CDT, catheter-directed thrombolysis; *PMT,* pharmacomechanical thrombectomy.

The variables are expressed as medians (range).

Table IV. One-year vein patency and symptom status. No significant differences were seen.

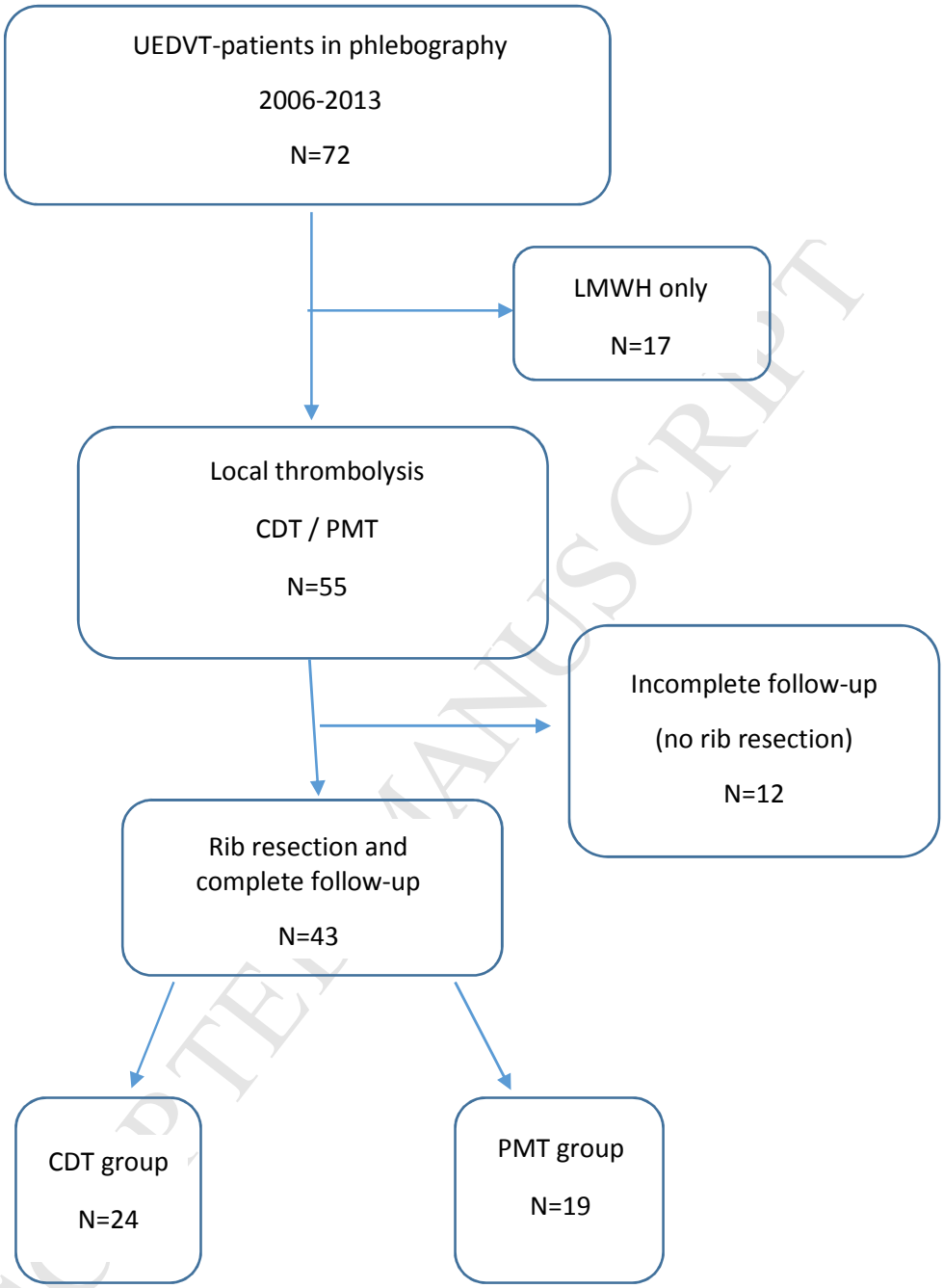
	PMT N = 19	CDT N = 24	p-value
Treatment method			
Good flow no lesion/stenosis <20%	17 (90%)	18 (75%)	*NS*
Moderate stenosis (20%-49%)	1 (5%)	2 (8%)	*NS*
Significant stenosis (50%/ > 50%)	0 (0%)	1 (4%)	*NS*
Occlusion	1 (5%)	3 (13%)	*NS*
Any PTA during the FU	10 (53%)	11 (46%)	*NS*
Good results of PTA	8/10 (80%)	10/11 (91%)	NS
Recoil/Failed PTA	2/10 (20%)	1/11 (9%)	NS
Patency in the final phlebography	18 (95%)	22 (92%)	*NS*
Symptoms assessment			
No symptoms	15 (79%)	16 (67%)	*NS*
Pain during rest	0 (0%)	0 (0%)	*NS*
Pain during exercise	1 mild (5%)	3 mild (13%)	*NS*
Swelling	1 mild (5%)	2 mild (8%)	*NS*
Numbness	2 mild (11%)	3 mild (13%)	*NS*
Paresthesia	0 (0%)	0 (0%)	*NS*
Weakness	0 (0%)	0 (0%)	*NS*
Complete improvement	15 (79 %)	16 (67%)	*NS*
No improvement	0 (0%)	0 (0%)	*NS*

Overall improvement	19 (100%)	24 (100%)	*NS*

NS, not significant; *CDT*, catheter directed thrombolysis; *PMT*, pharmacomechanical thrombectomy.

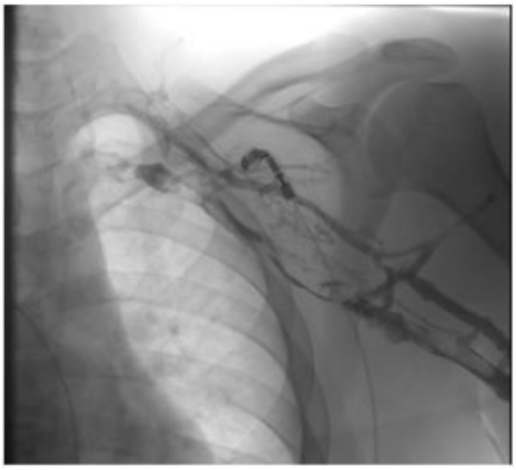
Values are reported as No. (%).

Figure 1.

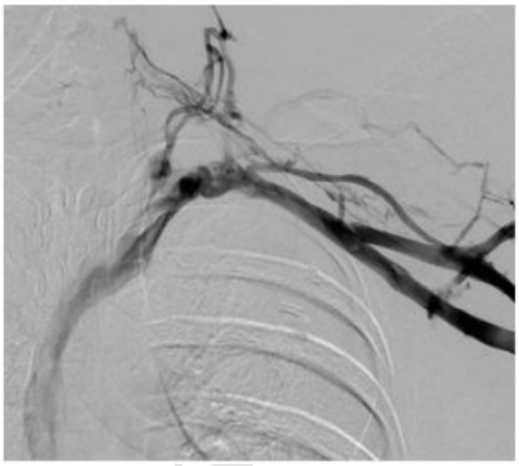


UEDVT = upper extremity deep venous thrombosis; CDT = catheter-directed thrombolysis; LMWH = low molecular weight heparin; PMT = pharmacomechanical thrombolysis

Figure 2.

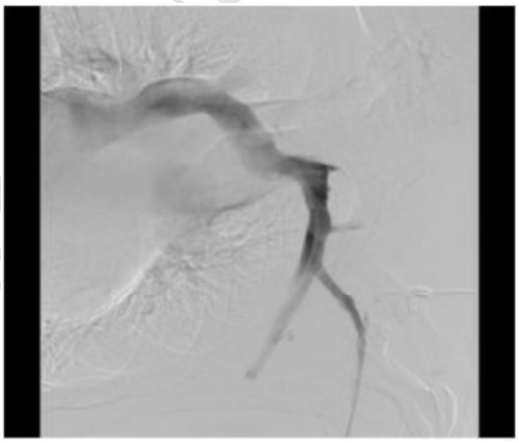


(A)



(B)

(C)



(D)